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Review Article

Personalized medicine: An overview

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ABSTRACT
Personalized medicine is a model for health care which is a combination of preventive, personalized, participatory and predictive measures. It is an approach for better treatment by identifying the disease causing genomic makeup of an individual. Personalized medicine is a broad field and it can be used for the diagnosis of various diseases like cancers, Alzheimer, Hepatitis, Cardiac diseases etc. It is an emerging field with lots of hope in the future. This review is basically based on characteristics of personalized medicine and its implementation in various diseases like lung cancer, renal cancer and rheumatoid arthritis. Further, the initiation taken by the European Union towards the development of personalized medicine and the challenges faced during the data collection, development of medicine and clinical trials were also discussed. The personalized medicine coalitions (PMC) have approved various novel medicines as personalized medicine under US FDA.

Keywords: Personalized medicine, genome, renal cancer, lung cancer, rheumatoid arthritis,

INTRODUCTION

Personalized medicine is a unique approach refers to a tailoring of medical treatment for the individual characteristics of patients. Personalized medicine is also known for precision medicine. These medicines are made based upon the genetic setup of human genome. It becomes the primary concern for the diagnosis, prevention and treatment of any disease and personalized medicine is based on the pharmacogenomics and genomics[1]. The advancement of molecular profile technology to get access on RNA, DNA and protein will potentiate the personalized medicine for managing the disease. Precision medicine having various advantages over conventional medicine like optimum therapy required, increase safety and efficacy, decrease adverse drug reaction, enhance patient compliance, reduce cost, time and clinical trials failure rate. Personalized medicine is a type of targeted treatment and it is helpful for wide spectrum of diseases like lung cancer, brain tumor, prostate cancer, rheumatoid arthritis, autoimmune diseases etc. This technology is also called for next generation sequencing (NGS). It is an evolving field where physicians use some diagnostic test for treating the patient and after combining both tests and medical history of patients, they can easily develop targeted medicine for individual patient[2].

PERSONALISED MEDICINE FOR LUNG CANCER

The systemic treatment for lung cancer is very limited, the targeted disease treatment is common now days and many more drugs and synthesis as well as approved like monoclonal antibody (mAbs) and tyrosine kinase inhibitors (TKIs). These are active against epidermal growth factor receptor (EGRF) and got response more than 70%[3]. According to further studies, it was observed that targeted drugs worsen the condition more than the cytotoxic drugs and these drugs are more costly than conventional drugs[4]. Non-small cell lung cancer (NSCLS) causes more number of cancers and these cells are having the characteristics of uncontrolled cell growth. An approach towards personalized medicine for cancer management is positron emission tomography (PET) and radioactive labeled drugs. Concentration of metabolite and pharmacokinetics was determined by regular assessment of blood sample urine etc[5].

The PET is a type of imaging technique used as a personalized medicine by utilizing gamma rays which produces 3 dimensional (3D) images[6]. The PET is having an advantage of targeting the diseased site by using radio labeled drugs which will further help in developing targeted drugs for the treatment as a personalized medicine. The pharmacokinetics (PK) of targeted drugs were studied and new medicine can be made and also binding of radio labeled drug with tumor can also predicted. Immuno-PET is a type imaging system that is mostly used as an antigen therapy. The MAbs had been investigated as an agent in Immuno-PET and mAbs are labeled with radionucleoids for example ^{89}Zr [7]. Because of slow PK, dynamic scanning was not possible in case of radio labeled mAbs. Static image utilizes the tumor-to-

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blood, standardized uptake value (SUV) and tumor-to-reference tissue ratios. After the binding of mAbs, target cell internalize the mAbs. Some radionucleoids get degraded and washed out from the cell such as ^{124}I, ^{76}Br etc[8].

The TKI-PET is also a tool for imaging damaged cells and it mostly targets the EGFR. TKI are tiny molecules having the rapid pharmacokinetic profiling which inhibits the activity of kinase proliferating path. For binding with target tyrosine kinase, TKI competes with ATP for example, EGFR kinase domain was targeted by erlotinib after competing with adenosine triphosphate (ATP) [9]. Typically; TKIs are labeled with ^{18}F or ^{11}C because of their short half-life activity they get better fit with biological half-life. After injecting the radio labeled TKIs, they get rapidly bind with the target cells and it frequently undergoes biliary and renal clearance. In this case, dynamic scanning is mostly used for assessment of PK modeling and uptake of quantitative tracing. There is an advantage of utilizing short live nucleotides is that it is easily decade and patient can take this therapy second time just after the first time[10]. The marketed personalized medicines are represented in Table 1.

Table 1: Marketed personalized medicine

Trade name of drug	Class of drug	Generic name of drug	Target site
Tarceva Iressa Tagrisso	Tyrosine kinase inhibitor	Erlotinib Gefitinib Osimertinib	Epidermal growth factor receptor
Portrazza	Monoclonal antibody	Necitumumab	
Avastin Cyramza		Bevasizumab Ramucirumab	Vascular endothelial growth factor receptor
keytruda		Pembrolizumab	Progressive disease

PERSONALISED MEDICINE FOR RENAL CARCINOMA

It is the most common problem facing by whole world especially Europe and deadliest problem there are two types of renal carcinoma one is renal pelvis carcinoma and other is renal cell carcinoma. 1000's of people are diagnosed with malignant tumor every year and the most common is nephroblastoma also called for Wilm's tumor (WT). The common symptoms are abdomen pain and swelling and it is mostly occur in children. Children oncology group (COG) identified the biomarker that is responsible for nephroblastoma. Doxorubicin (DOX) with Vincristine (VCR) and Actinomycin-D (ACT-D) was given to the stage I, and II patients but there was no significant effect [12].

In preclinical testing authors observed that after targeting the Insulin growth factor (IGF) pathway by IMC-A12 (monoclonal antibody), there was arrest in cell cycle as well as reduction in size of tumor. It depicted the good antitumor activity and can be effective for rhabdomysarcoma patient also[13]. Weiqel et al, aimed their study to know the effectiveness of cixutumumab. The drug (9 mg/kg) through intravenous route was administered to the patients and it was observed that children tolerated cixutumumab easily and better agent for IGF inhibition[14].

For early detection of tumor a combine therapy (drug and antibody) was employed by Wood et al. An example of this combination system is lorvotuzumab mertansine, conjugation of cytotoxic and mAbs to CD-56 which shows good antitumor activity against WT xenografts[15].

There is 50-70% subjects suffering from clear cell renal cell carcinoma (ccRCC), the pathophysiology of treatment is to target the Von hipple lindau (VHL) and inactivation of components present in signaling pathway. The VHL is a biomarker that is responsible for renal carcinoma and other markers are carbonic anhydrase and VEGF. The recently developed personalized medicines are bevacizumab for bevicizumab, axitinib, sorafinib, and temsirolimus[16]. Now some people became resistant to these medicines and sunitinib is the commonly used first line drug for treatment. So, for overcoming to this problem and also for enhancing the efficacy of RCC therapy drugs should be combined with antiangiogenic agent. Xu et al, patient get treated by pazopanib and they observed that there is an association between Single nucleotide polymorphism (SNP) and progression free survival and higher response as compared to earlier treatment[17].

Renal cell carcinoma (RCC) initiatives

Cancer genomic of the kidney consortium (CAGEKID) consisting 14 members from the 6 different countries of EU is an initiative to analyze the epigenetic, genetic and transcriptomic feature in ccRCC. Initially characterized 100 patients and for other two phases 400 and 2300 patients have been characterized[19]. Biomarker pipeline, a part of National Institute for Health and Research has selected 600 participants from 10 UK centers and sampling of fluid and tissue sample have been analyzed as per standard operating procedure. The main focus of this initiative is to evaluate the existing data and longitudinal and prognosis monitoring of protein biomarkers for future and existing assays[20]. In target therapy for renal carcinoma, genetic biomarker is used for the response and toxicity of the drug treatment. It is a European collaboration, which consists of 12 members of 8 different countries. This initiation is based on the methylation, tumor gene compression and germ line genome[21]. Scottish collaboration on translational research (SCOTR), a Scotland base initiative has objective to banking of clinical samples which are obtained from the newly diagnosed patients[22].

PERSONALISED MEDICINE FOR RHEUMATOID ARTHRITIS

Table 2: Status of approved personalized drugs

Drug name	Disease	Approval year
Crizonitinib	Non-small cell lung cancer	2013
Erlotinib	Non-small cell lung cancer	2013
Lynparza	Ovarian cancer	2014
Vimizim	Mucopolysaccharidosis	2014
Cyrazma	Non-small cell lung cancer	2014
Zykadia	Non-small cell lung cancer	2014
Beleodaq	T- cell lymphoma	2014
Cerdelga	Gaucher disease type I	2014
Harvoni	Hepatitis C	2014
Viekera	Hepatitis C	2014
Blincyto	Acute lymphoblastic lymphoma	2014
Nucala	Asthma	2015
Cotellic	Melanoma	2015
Aristada	Schizophrenia	2015
Lonsurf	Colorectal cancer	2015
Repatha	Hypercholesterolemia	2015
Daklinza	Hepatitis C	2015
Rexulti	Schizophrenia	2015
Orkambi	Cystic fibrosis	2015
Ibrance	Breast cancer	2015
Alecensa	Non-small cell lung cancer	2015
Tagrissco	Non-small cell lung cancer	2015

Koczan et, al, The main aim of his study was to identify the biomarkers which will predict the outcomes of therapy in rheumatoid arthritis patient who get treated by TNF-α blocker i.e., etanercept. They selected 19 RA (Rheumatoid arthritis) patients and out of those, 7 patients are non-responders and 12 patients are responders and changes in pre existing genes were monitored. The Affymetrix microarray generated a result, which was compared with post treatment analyzed data. After 72 hours of treatment, gene expression get changed and shows good (DAS) disease activity score i.e., 28 >1.2. Some patient develops Interferon (IFN), which shows worse response to the treatment. Therefore, it is concluded that early prediction of RA response is possible when TNF-α blocker is administered based on their gene expression and better medication can be given according to their gene setup[23].

Lequerre et al, studied effect of combination of drug methotrexate and infliximab, response was observed after three months. They have selected 13 patients and gene profiling was done, by using mononuclear cells of peripheral blood. Out of those selected patients, 7 patients are non responder and 6 patients are responder to the treatment. There is a hybridization of baseline RNAs and transcription of mRNA. Difference in transcription level was compared with response and down regulation was observed in non responders. There are 279 genes which are expressed differently in case of respondents and non-respondents[24].

PERSONALISED MEDICINE AND ITS CHALLENGES

There are various challenges in the field of personalized medicines[25]. Some are as follows:

Insufficient Understanding of Internal Biology of Disease

This field is not known to all, people are not much aware about the concept of personalized medicine. People thought that Conventional medicines are sufficient for the treatment; another reason is insufficient knowledge about the genetic makeup of person and the biomarkers responsible for the disease.

Limited Infrastructure

It is main aspect that should be consider during the preparation of personalized medicine, the requirement of accessories or computerized during the gene detection or manipulation need more time as well as money also. Because of this reason also there is lack of information about the gene sequencing or setup of gene. For establishing an infrastructure of any work fund is a most important requirement.

Classification of Disease

It acknowledges that the classification system is too outdated and diseases mostly all the diseases comes under same class and based on their sign and symptoms they are classified. Accommodation of emerging information of any disease is not easy in this system therefore, subtype of any disease with different molecular factors is considered as same disease. This outdated classification of disease systems became the barrier for the entry of personalized medicine. National Academy of science called for a new creation called new taxonomy of all disease which will enhance and update the understanding of pathogenesis of disease and also improve the human health. This will also give information about the intrinsic biology as well as the sign and symptoms of any disease.

Accessibility of Personalized Medicine to the Patients

It is a newer approach towards the diagnosis and treatment of disease and most of the people get benefit when they get diagnosed based on their genetic makeup and also they get treated but still most of the population is unaware about this. Because of this problem all people are not get diagnosed or treated so, the initiative should be reach to all people and increase the awareness about the precision medicine.

Implementation of Newer Diagnostics

Clinically it is difficult for the people as well as physicians to apply new technique when older therapies are already present. It is difficult for them to interpret, identify and order and the overloading of information is also a problem, it makes the adoption difficult during new testing without any decision[25].

FDA APPROVAL OF PERSONALISED MEDICINE

After the initiation of personalized medicine there is a transformation of one to all to one for individual, which

refers to targeting of disease by utilizing the molecular information, which accelerates the United States Food and Drug Administration (US FDA) frequently approves the precision medicine (Table 2). Center for drug and research (CDER) has approved 45 drugs out of those 13 new novel drugs approved as personalized medicine i.e., more than 25% in 2015 and the classification is done by personalized medicine coalition (PMC). In 2014, FDA approved 9 medicines out of 41 as personalized medicine i.e., 20%. According to PMC personalized medicine are those products whose label contains particular biomarker for an individual that will help in decision-making or procedure for the use by individual patient[26, 27].

CONCLUSION AND FUTURE PERSPECTIVES

Precision medicine is getting attention for its potential and uniqueness with its upcoming new opportunities. The personalized medicine is based on the discovery of individual genes, which cause disease. Pharmacogenomics is a promising field but it's a best method to create new targeted therapy for any disease. Because of this approach we will get accuracy in the treatment and also the chances of side effects will also be reduced. This could be a better way to reduce the cost and time required to develop new medicine. Now, people believing on system which will ultimately increases the popularity. This initiative is not reach to all parts but slowly this will be helpful for developing countries also. This sophisticated approach could be a hope for the development of robustive novel biologics or bio-markers for disease management. The FDA has already approved so many medicines and in future also it will approve based on their novelty. This therapy is a combination of clinical and family history which offers the exciting and novel tool for drug development. As it is a challenging field, this could be tough to overcome all the problems because of its expensiveness, insufficient information, less awareness to the people etc. The development of therapies could be a tough job for all because it need more time to developed and need sophisticated commercial assay technique but at other side it might be beneficial for developing counties. So, the personalized medicine can be a better approach for early detection and cure of disease but for this people or future physician should be response and active towards the work so they can easily face the challenges and make this approach feasible to all.

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